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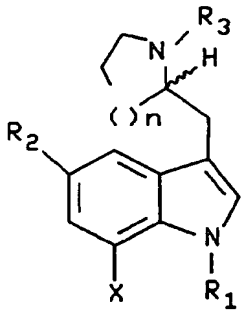
(71) Applicant: **PFIZER INC.**
New York, N.Y. 10017 (US)

(72) Inventors:
- **Macor, John Eugene**
  Penfield, New York 14526 (US)
- **Wythes, Martin James**
  Sandwich, Kent (GB)

(74) Representative: **Wood, David John et al**
PFIZER LIMITED,
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(54) Indole derivatives

(57) Compounds of the formula



I

wherein n is O, 1, or 2; X is chlorine, bromine, or iodine; R_1 is hydrogen; R_2 is selected from hydrogen, halogen, cyano, $-OR_4$, $-(CH_2)_m-(C=O)NR_5R_6$, $-(CH_2)_m-SO_2NR_5R_6$, $-(CH_2)_m-NR_7(C=O)R_8$, $-(CH_2)_m-NR_7SO_2R_8$, $-(CH_2)_m-S(O)_xR_8$, $-(CH_2)_m-NR_7(C=O)NR_5R_6$, $-(CH_2)_m-NR_7(C=O)OR_9$, and $-CH=CH(CH_2)_yR_{10}$; R_3 is selected from hydrogen and C_1 to C_6 linear or branched alkyl, and the pharmaceutically acceptable salts thereof are new. These compounds are useful psychotherapeutics and are potent serotonin (5-HT_1) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators. A process for forming indoles by transition metal catalyzed cyclization of a dihalogenated intermediate.

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Description

The present invention relates to indole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating migraine and other disorders.

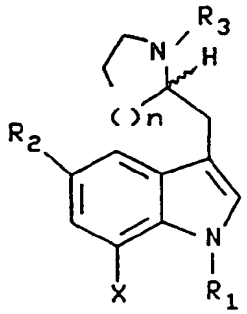
United States Patents 4,839,377 and 4,855,314 and European Patent Application Publication Number 313397 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

British Patent Application 040279 refers to 3-aminoalkyl-1H-indole-5-thioamides and carboxamides. The compounds are said to be useful in treating hypertension, Raymond's disease and migraine.

European Patent Application Publication Number 303506 refers to 3-poly:hydro-pyridyl-5-substituted-1H-indoles. The compounds are said to have 5HT1-receptor agonist and vasoconstrictor activity and to be useful in treating migraine.

European Patent Application Publication Number 354777 refers to N-piperidinyl:indolyl:ethyl-alkane sulfonamide derivatives. The compounds are said to have 5HT1-receptor agonist and vasoconstrictor activity and to be useful in treating cephalic pain.

The present invention relates to compounds of the formula



I

wherein n is O, 1, or 2; X is chlorine, bromine, or iodine; R_1 is hydrogen; R_2 is selected from hydrogen, halogen (e.g., fluorine, chlorine, bromine or iodine), cyano, $-OR_4$, $-(CH_2)_m-(C=O)NR_5R_6$, $-(CH_2)_m-SO_2NR_5R_6$, $-(CH_2)_m-NR_7(C=O)R_8$, $-(CH_2)_m-NR_7SO_2R_8$, $-(CH_2)_m-S(O)_xR_8$, $-(CH_2)_m-NR_7(C=O)NR_5R_6$, $-(CH_2)_m-NR_7(C=O)OR_9$, and $-CH=CH(CH_2)_yR_{10}$; R_3 is selected from hydrogen and C_1 to C_6 linear and branched alkyl; R_4 is selected from hydrogen, C_1 to C_6 alkyl, and aryl; R_5 and R_6 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl or R_5 and R_6 taken together to form a 4, 5, or 6 membered ring; R_7 and R_8 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_9 is selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_{10} is selected from $-(C=O)NR_5R_6$ and $-SO_2NR_5R_6$, wherein R_5 and R_6 are defined as above, and $-NR_7(C=O)R_8$, $-NR_7SO_2R_8$, $-NR_7(C=O)NR_5R_6$, $-S(O)_xR_8$ and $-NR_7(C=O)OR_9$, wherein R_7, R_8, and R_9 are as defined above; m is 0, 1, 2, or 3; y is 0, 1, or 2; x is 1 or 2; and the above aryl groups and the aryl moieties of the above alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen (e.g., fluorine, chlorine, bromine or iodine), hydroxy, cyano, carboxamido, nitro and C_1 to C_4 alkoxy, with the proviso that when R_2 is hydrogen or $-OR_4$ and R_4 is hydrogen, n is 0 or 1, and the pharmaceutically acceptable salts thereof. These compounds are useful in treating migraine and other disorders. Compounds of the formula I wherein R_2 is $-CH=CH(CH_2)_yR_{10}$ and compounds of formula I where X is chlorine, bromine, or iodine are also useful as intermediates for preparing other compounds of the formula I.

The compounds of the invention include all optical isomers of formula I (e.g., R and S enantiomers) and their racemic mixtures. The R enantiomers at the designated chiral site in formula I are preferred.

Unless otherwise indicated, the alkyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g. alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) or be linear or branched and contain cyclic moieties.

Preferred compounds of the invention are compounds of the formula I wherein R_1 is hydrogen; R_2 is $-(CH_2)_m-SO_2NHR_5$, $-(CH_2)_m-NHSO_2R_8$, $-(CH_2)_m-SO_2R_8$, $-(CH_2)_m-(C=0)NHR_5$, or $-(CH_2)_m-NH(C=0)R_8$; R_3 is hydrogen or methyl; and m, R_5 and R_8 are as defined above and the pharmaceutically acceptable salts thereof. Of the foregoing preferred compounds, the R enantiomers at the designated chiral site in formula I are more preferred.

The following compounds are preferred:

(R)-7-Bromo-5-(t-butylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole; and

(R)-7-Bromo-5-(methylaminosulfonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

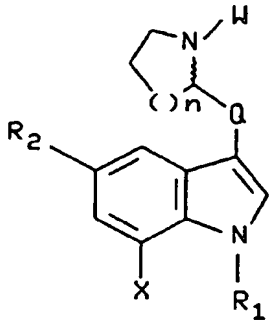
The present invention also relates to a pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition and a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition and a pharmaceutically acceptable carrier.

The present invention also relates to a method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

The present invention also relates to a method for treating disorders arising from deficient serotonergic neurotransmission (e.g., depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders) comprising administering to a mammal (e.g., a human) requiring such treatment an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating such condition.

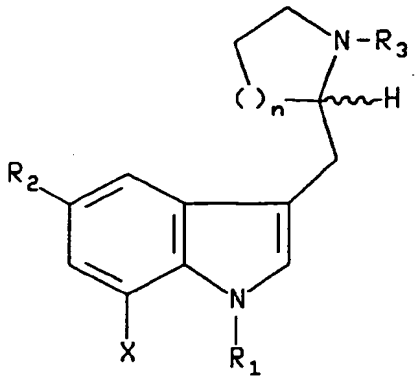
The present invention also relates to a compound of the formula



V

wherein X is bromine, chlorine, or iodine; W is $-CO_2R_{11}$ or R_3; Q is CH_2 or C=O; n, R_1, R_2 and R_3 are as defined for formula I; and R_{11} is selected from C_1 to C_6 alkyl, benzyl and aryl, wherein aryl is as defined above, with the proviso that when W is R_3, Q is C=O, and with the proviso that when X is bromine, chlorine, or iodine, W is $-CO_2R_{11}$ and Q is CH_2. The compounds of formula V are useful as intermediates in preparing compounds of the formula I.

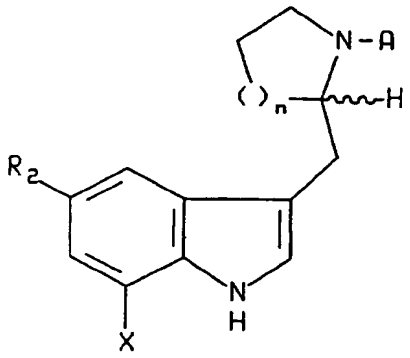
Compounds of formula I are prepared by catalytic reduction of a compound of the formula



(XV)

wherein R^3 is as defined above or is a substituent of the formula $-CO_2-R_q$, R_q is benzyl or substituted benzyl, and where R^1, R^2, and n are as defined above and X is chlorine, bromine or iodine (preferably bromine or iodine) under an atmosphere of hydrogen, preferably at a pressure of about 1 to 4 atmospheres, or using a hydrogen source such as ammonium formate or formic acid in an inert solvent. Suitable catalysts include 20% palladium (II) hydroxide on carbon, palladium on carbon, Raney nickel, platinum oxide, rhodium and ruthenium. The preferred catalyst is 20% palladium (II) hydroxide on carbon. Suitable solvents include C_1 to C_6 alcohols, N, N-dimethylformamide, ethyl acetate and acetonitrile. The preferred solvent is ethanol. The reaction is generally conducted at a temperature of about 0°C to about 60°C, most preferably at about 25°C.

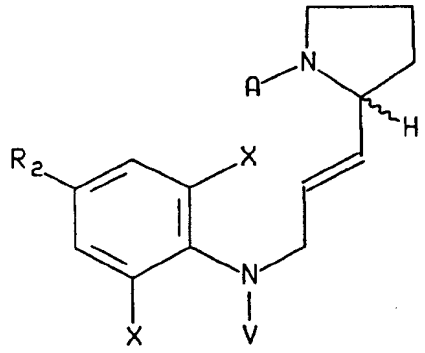
Compounds of formula XV are prepared by hydride reduction of a compound of the formula



(XVI)

wherein R_2 and n are as defined above and A is a suitable nitrogen protecting group and X is chlorine, bromine or iodine (preferably bromine or iodine) with a hydride reducing agent in an inert solvent. Suitable hydride reducing agents include lithium aluminum hydride, diborane, lithium borohydride, and sodium amide. The preferred reagent is lithium aluminum hydride. Suitable solvents include ethers, such as diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane. The preferred solvent is tetrahydrofuran. The reduction is conducted at a temperature of about 30°C to about 100°C, preferably about 65°C to about 70°C. Examples of A include t-butoxycarbonyl (BOC) and benzyloxycarbonyl (CBZ), preferably CBZ (See T. W. Green, Protecting Groups in Organic Synthesis, John Wiley & Sons (1981) pp 218-287). A side product of this reaction can be a compound of formula I where X is hydrogen and R_3 is methyl.

Compounds of formula XVI can be prepared by the transition metal catalyzed cyclization of a compound of the formula

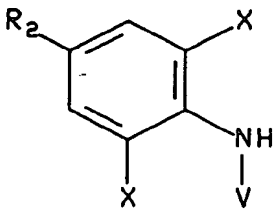


(XVII)

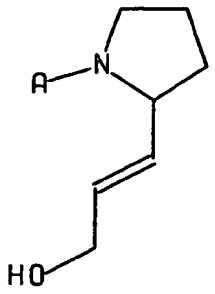
wherein R_2, n, A, and V are as defined above, and X is chlorine, bromine or iodine (preferably bromine or iodine) and R_{12} is $-OR_{11}$ as defined above or alkyl, aryl, or trifluoromethyl (preferably trifluoromethyl) in a suitable inert solvent with a phase transfer catalyst, a base and a suitable transition metal catalyst. Suitable transition metal catalysts include palladium salts such as palladium (II) acetate or palladium (II) chloride (preferably palladium acetate) and rhodium salts, such as tris(triphenyl)rhodium (I) chloride. Suitable solvents include N,N-dimethylformamide, N,N-dimethylformamide with dimethoxyethane, acetonitrile, and N-methylpyrrolidine. The preferred solvents are N,N-dimethylformamide and N,N-dimethylformamide with dimethoxyethane. Suitable phase transfer catalysts include tetraalkylammonium halides,

preferably tetra-n-butylammonium chloride. Suitable bases include tertiary amines, sodium hydrogen carbonate, and sodium carbonate. The preferred base is triethylamine. The reaction is conducted at a temperature of about 80°C to about 180°C, preferably about 150°C to 160°C. Examples of V include t-butoxycarbonyl-(BOC), benzyloxycarbonyl(CBZ), and trifluoroacetyl, preferably trifluoromethylacetyl (See T. W. Green, Protecting Groups in Organic Synthesis, John Wiley & Sons (1981) pp 218-287).

Compounds of formula XVII can be prepared by the Mitsunobu coupling reaction of compounds of formulae



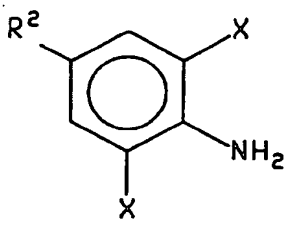
(XVIII)



(XIX)

wherein R_2, V, A and X are as defined above using a phosphine and an azodicarboxylate in a suitable solvent. Suitable phosphines include trialkylphosphines and triarylphosphines, preferably triphenyiphosphine. Suitable azodicarboxylates include dialkyl azodicarboxylates, preferably diethyl azodicarboxylate. Suitable solvents include methylene chloride, ethers, including tetrahydrofuran, diethyl ether, and 1,4-dioxane, N-N-dimethylformamide and acetonitrile. The preferred solvent is tetrahydrofuran. The reaction is conducted at a temperature of about 0°C to about 65°C, most preferably at about 25°C.

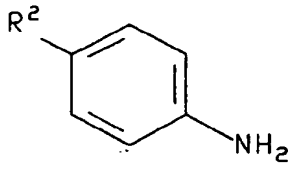
Compounds of formula XVIII, if not available commercially, can be prepared by reacting a compound of formula



(XX)

wherein R_2 and X are as defined above with the acid chloride or the symmetrical carboxylic anhydride of the formula V-O-V, where V is as defined above, in a suitable solvent with a suitable base. The preferred acid chloride or anhydride is trifluoroacetic anhydride. Suitable solvents include ethers, including tetrahydrofuran, diethyl ether and 1,4-dioxane, methylene chloride, and chloroform. The preferred solvent is methylene chloride. Suitable bases include triethylamine, pyridine, and sodium hydrogen carbonate. The preferred base is pyridine. The reaction is conducted at a temperature of about 0°C to about 65°C, preferably at about 25°C.

Compounds of formula XX, if not available commercially, can be prepared by reacting a compound of formula



(XXI)

wherein R_2 is as defined above with either chlorine, bromine or iodine in a suitable solvent with a suitable base using two equivalents of halogen. Reaction with bromine is preferred. Suitable solvents include C_1-C_6 alcohols, methylene chloride, methanol with methylene chloride, chloroform, or carbon tetrachloride. The preferred solvents are methanol and methanol with methylene chloride. Suitable bases include triethylamine, pyridine, sodium carbonate, and sodium

hydrogen carbonate. The preferred base is sodium hydrogen carbonate. The reaction is conducted at a temperature of about 0°C to about 65°C, preferably at about 25°C.

Unless indicated otherwise, the pressure of each of the above reactions is not critical. Generally, the reactions will be conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. If necessary, upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, e.g., where R_2 contains a carboxylate, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction of maximum product of yields of the desired final product.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as the active compounds of the invention) are useful psychotherapeutics and are potent serotonin (5-HT_1) agonists and may be used in the treatment of depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, chronic paroxysmal hemicrania and headache associated with vascular disorders, pain, and other disorders arising from deficient serotonergic neurotransmission. The compounds can also be used as centrally acting antihypertensives and vasodilators.

The active compounds of the invention are evaluated as anti-migraine agents by testing the extent to which they mimic sumatriptan in contracting the dog isolated saphenous vein strip (P.P.A. Humphrey et al., Br. J. Pharmacol., 94, 1128 (1988)). This effect can be blocked by methiothepin, a known serotonin antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anaesthetized dog. It has been suggested (W. Fenwick et al., Br. J. Pharmacol., 96, 83 (1989)) that this is the basis of its efficacy.

EC_{50}'s for the compounds of formula I tested for contracting the dog isolated saphenous vein strip, using the procedure referred to above, were less than 10^{-4} M.

The active compounds of the present invention are also evaluated via the inhibition of plasma protein extravasation response within the dura mater of guinea pigs following unilateral electrical trigeminal ganglion stimulation. The extent to which they mimic sumatriptan, in terms of both potency and efficacy, is determined in this assay. The procedure is performed on male Hartley guinea pigs (200-250 g, Charles River Laboratories, Wilmington, MA, U.S.A.) as described in Markowitz et al., J. Neurosci., 7 (12), 4129-4136 (1987) and also in Lee, et al., Brain Research, 626, 303-305 (1993). The procedure briefly consists of placing pentobarbitone-anesthetized animals in a stereotaxic frame. ^{125}I-BSA (bovine serum albumin) (50 $\mu Ci/kg^{-1}$) is first injected into the femoral yein, followed 5 minutes later by drug or vehicle. Bipolar electrodes are then lowered into the trigeminal ganglia, and the right ganglion is stimulated for 5 minutes (1.2 mA, 5 Hz, 5 msec). The animal is then perfused with saline through the left cardiac ventricle and sacrificed, and the dura mater is dissected, weighed, and counted for radioactivity. Cpm/mg wet weight values are determined for the right vs left dura mater, and a ratio for the stimulated vs unstimulated sides is generated for each animal. Unpaired student's t-test is used to statistically compare these ratio values in respective groups treated with vehicle or drug. The M.E.D. (minimally effective dose) for a given compound is the lowest dose for which the mean value of this ratio is significantly lower than that obtained for the vehicle-treated group. The effect of the drugs in these assays can be partially blocked by metergo-

line, a known serotonin antagonist.

A similar procedure to the one described above can be performed on rats, as described in Matsubara, et al., Br. J. Pharmacol., 104, 3 (1991).

The active compounds of the invention may also be useful in the treatment of headache associated with meningeal irritation, including bacterial, fungal, viral, parasitic, and chemical meningitis, acquired immune deficiency syndrome (AIDS) meningovascular inflammation, and subarachnoid hemorrhage. [See W. S. Lee, et al., Evidence Using Conformationally Restricted Sumatriptan Analogues, CP-122,288 and CP-122,638, that 5-HT_{1D} Receptors Do Not Mediate Blockade of Neurogenic Inflammation, 23rd Annual Meeting of the Society for Neuroscience, Washington, D.C., November 7-12, 1993, Abstract #565.6; K. Nozaki, et al., CP-93,129, Sumatriptan, Di-hydroergotamine Block c-fos Expression Within Rat Trigeminal Nucleus Caudalis Caused by Chemical Stimulation of The Meninges, Br. J. Pharmacol. (1992), 106, 409; and Lee, et al, Brain Research, 626, 303-305 (1993).]

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the present invention may be useful in the treatment of a considerable number of diseases. These include dermatological disorders, including psoriasis; eczema and atopic eczematous dermatitis; intractable itch (pruritus), including itch associated with liver cirrhosis, cancer and hemodialysis; burns and scalds; sunburn; insect bites, urticaria and sweat gland abnormalities. Other dermatological disorders include bullous penphgoid, photo dermatoses, skin blisters, adult acne, chicken pox and dermatitis herpetifunus.

Other diseases which may be treated with the compounds of the present invention are peripheral neuropathies including postherpetic neuralgia, diabetic neuropathies such as peripheral polyneuropathy and radiculopathy; causalgia and reflex sympathetic dystrophy; post-mastectomy neuralgia; post-surgical neuralgia and pain; vulvar vestibulitis; phantom limb pain; thalamic syndrome (central post-stroke pain); temporo mandibular joint syndrome; metarsalgia (Morton's neuralgia); and neurogenic pain from nerve compression caused, for example, by a prolapsed intervertebral disc or carpal and tarsal tunnel syndromes.

The above-mentioned compounds may also be useful in alleviating arthritis, including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia, ankylosing spondilitis and tendinitis. They are also effective against gastrointestinal and urogenital diseases including cystitis, gastroesophageal reflux, gastritis, urge continence, inflammatory bowel disease and irritable bowel syndrome; they are effective in regulatory gastrointestinal tract motility.

The compounds may also be used in the treatment of headache associated with substances or their withdrawal (e.g. drug withdrawal), tension headache, pediatric migraine and prophylaxis of migraine and post-traumatic dysautonomic cephalgia.

They may also be used for treating orificial pain (for example toothache and pain of dental origin, earache, TMJ pain, sinus pain, myofacial pain, non-arthritic and non-musculoskeletal cervical pain), mouth ulcers, Meniere's disease and atypical facial neuralgia, and also allergic and chronic obstructive airways diseases such as rhinitis, conjunctivitis, bronchial oedema, bronchial asthma, neurological pulmonary oedema (adult respiratory disease syndrome), anaphylaxis and angioedema. The compounds are also efficacious in treating ocular pressure or glaucoma and ocular inflammation.

It is believed that the compounds of formula I and their salts are efficacious against emesis caused by several factors not associated with migraine, including emesis induced by anaesthesia, cancer chemotherapy and by motion (seasickness, space and airsickness).

The activity of the compounds as anti-emetics may be demonstrated by the method of Tatersall et al and Bountra et al (European Journal of Pharmacology, 250 (1993) R5 and 249 (1993) R3-R4). In this method the extent to which they reduce the latency or the number of retches and/or vomits induced by emetogins in the conscious ferret compared to vehicle - treated animals is measured. It is found that the compounds are effective against emesis caused by a wide range of emetogeny, extending from local irritants to anti-cancer radiation treatment.

Compounds of formula I described above but for the fact that one or more hydrogen, oxygen, or nitrogen atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research or diagnostic tools in metabolism pharmacokinetic studies and in binding assays. Specific applications could include the discovery of novel receptors involved in the pathogenesis of neurogenic inflammation, leading to diseases such as migraine. Isotopes included among the radiolabelled forms of these compounds are the ^{3}H and ^{14}C isotopes thereof (e.g. the 7-^{2}H, 7-^{3}H, and N-($^{3}H_3$)-methyl[i.e., having CT_3 on the pyrrolidinyl nitrogen]), for example, (R)-N-methyl-3-(1-methyl-2-pyrrolidinylmethyl)-1H-[7-^{2}H]-indol-5-yl]methanesulfonamide, (R)-N-methyl-[3-(1-methyl-2-pyrrolidinylmethyl)-1H-[7-^{3}H]-indol-5-yl]methanesulfonamide, and (R)-N-methyl-[3-(1-($^{3}H_3$)methyl-2-pyrrolidinylmethyl)-1H-indol-5-yl]methanesulphonamide. The 7-^{2}H and 7-^{3}H derivatives of the invention can be prepared by the deuteration or tritiation of the corresponding 7-bromo-derivative, preferably in the presence of pre-reduced Pearlman's catalyst in an organic solvent such as ethanol. The $^{3}H_3$ (i.e., tri-tritiated derivative) can be prepared by the reaction of the corresponding compound having no substitution on the pyrrolidinyl nitrogen, preferably as a salt such as the hydrobromide, with $^{3}H_3$ methyl iodide, prefera-

bly in the presence of a base such as potassium carbonate.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate) ; lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μg to 1000 μg of the other compounds of the invention. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The above-cited ranges will generally be those most desirably employed in the administration of the, active compounds. Nevertheless, variations may still occur depending on the age, weight, the patient's individual response to the compound being administered, as well as the severity of the condition for which he, or she, is being treated and the type of pharmaceutical formulation chosen and time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid ranges may be more than adequate, while in other cases still larger doses may be employed without causing harmful side effects provided that such higher dose levels are first divided into small doses for administration throughout the day.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Specific rotations were measured at room temperature using the sodium D line (589 nm).

Commercial reagents were utilized without further purification. Chromatography refers to column chromatography performed using 32-63 μm silica gel and executed under nitrogen pressure or compressed air pressure (flash chromatography) or gravity conditions. Room temperature refers to 20 - 25°C.

EXAMPLE 1

General Procedure for the Reduction of Benzyloxycarbonyl- pyrrolidin-2-ylcarbonyl-1H-Indole, N-Benzyloxycarbonyl-azetidin-2-ylcarbonyl-1H-Indoles, or N-Benzyloxycarbonyl-piperidin-2-ylcarbonyl-1H-Indoles Forming 3-(N-Methyl- pyrrolidin-2-ylmethyl)-1H-Indoles, 3-(N-Methylazetidin-2-ylmethyl)-1H-Indoles, or 3-(N-Methylpiperidin-2-ylmethyl)-1H-Indoles, respectively.

To a stirred solution of (R)- or (S)-(N-benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-1H-indole, (R)-, (S), or (R,S)-(N-benzyloxycarbonylazetidin-2-ylcarbonyl)-1H-indole, or (R)-, (S)-, or (R,S)-(N-benzyloxycarbonylpiperidin-2-ylcarbonyl)-1H-indole, (5.00 mmol) in anhydrous tetrahydrofuran (20mL) at room temperature under nitrogen was carefully added lithium aluminum hydride (0.57 g, 15.0 mmol, 3.0 eq) as a powder, and the resulting mixture was stirred at room tem-

perature under nitrogen for 1 hour. The mixture was then heated at reflux (66°C) under nitrogen for 12 hours. The reaction was then quenched with successive additions of water (0.5 mL), aqueous sodium hydroxide (20%, 0.5 mL), and then additional water (1.0 mL), and the resulting mixture filtered through diatomaceous earth (Celite (trademark)). The solids were then washed with copious amounts of ethyl acetate (50 mL). The combined filtrate was then washed with water (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was then column chromatographed using silica gel (50 g) and elution with the appropriate solvent system to afford the 3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, 3-(N-methylazetidin-2-ylmethyl)-1H-indole, or 3-(N-methylpiperidin-2-ylmethyl)-1H-indole. Following this procedure the following compounds were prepared:

A. (S)-5-Methoxy-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

(S)-(N-Benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-methoxy-1H-indole was used. The chromatographic eluent was 8% triethylamine in ethyl acetate to afford the title compound (yields ranged from 22 to 57%) as an oil: IR ($CHCl_3$) 3475, 1625, 1585, 1480, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (br s, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.04 (d, J=2.4 Hz, 1H), 6.97 (d J=2.2 Hz, 1H), 6.84 (dd, J=2.4 and 8.8 Hz, 1H), 3.86 (s, 3H), 3.17-3.10 (m, 2H), 2.58 (dd, J=9.9 and 13.9 Hz, 1H), 2.50-2.40 (m, 1H), 2.47 (s, 3H), 2.26-2.17 (m, 1H), 1.89-1.72 (m, 2H), 1.70-1.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.8, 131.4, 128.2, 122.7, 113.9, 111.8, 111.7, 101.1, 66.6, 57.5, 56.0, 40.8, 31.5, 30.0, 21.9; LRMS, m/z (relative intensity) 244 (M^+, 7), 160 (20), 145 (16), 117 (21), 84 (100); HRMS: calculated for $C_{15}H_{20}N_2O$: 244.1573; found: 244.1575; $[\alpha]^{25}_D$ = -96° ($CHCl_3$, c = 1.0).

B. (R)-5-Methoxy-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

(R)-(N-Benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-methoxy-1H-indole was used. The chromatographic eluent was 8% triethylamine in ethyl acetate to afford the title compound (yields ranged from 13 to 61%) as an oil whose spectral and physical properties were identical with the spectral and physical properties of the title compound of Example 1A with the exception of specific rotation of plane polarized light: $[\alpha]^{25}_D$ = + 100° ($CHCl_3$, c = 1.0). HRMS: calculated for $C_{15}H_{20}N_2O$: 244.1573; found: 244.1547.

C. (R)-5-Dibenzylamino-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

(R)-3-(N-Benzyloxycarbonylpyrrolidin-2-ylcarbonyl)-5-dibenzylamino-1H-indole was used. Column chromatography using elution with methylene chloride/methanol/ammonium hydroxide [9:1:0.1] afforded the title compound as a pale green foam: ^1H NMR ($CDCl_3$) δ 7.82 (br s, NH), 7.35-7.19 (m, 10 H), 7.20 (d, J=8.6 Hz, 1H), 6.95 (d, J=2.1 Hz, 1H), 6.85 (dd, J=2.3 and 8.7 Hz, 1H), 6.80 (d, J=2.2 Hz, 1H), 4.65 (s, 4H), 3.25-3.02 (m, 2H), 2.52 (dd, J=9.5 and 13.9 Hz, 1H), 2.39-2.15 (m, 2 H), 2.30 (s, 3H), 1.85-1.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 143.2, 139.7, 130.5, 128.5, 128.2, 127.3, 126.8, 122.9, 112.5, 112.2, 111.8, 103.4, 67.0, 57.4, 56.4, 40.6, 31.4, 29.7, 21.9. HRMS: calculated for $C_{28}H_{31}N_3$ 409.2520. Found 409.2475.

D. (R)-5-Methoxy-3-(N-methylpiperid-2-ylmethyl)-1H-indole

(R)-3-(N-Benzyloxycarbonylpiperid-2-ylcarbonyl)-5-methoxy-1H-indole was used. Column chromatography using elution with 6% triethylamine in ethyl acetate afforded the title compound as a white foam: ^{13}C NMR ($CDCl_3$) δ 153.7, 131.4, 128.3, 123.3, 113.2, 111.7, 111.6, 101.2, 64.4, 57.2, 55.9, 43.4, 31.0, 28.8, 25.9, 24.1; $[\alpha]^{25}_D$ = +67° ($CDCl_3$, c=1.0); HRMS: calculated for $C_{16}H_{22}N_2O$: 258.1734. Found: 258.1710.

E. (S)-5-Methoxy-3-(N-methylazetidin-2-ylmethyl)-1H-indole

(S)-3-(N-Benzyloxycarbonylazetidinyl-2-ylcarbonyl)-5-methoxy-1H-indole was used. The chromatographic eluent was 8% triethylamine in ethyl acetate to afford the title compound as a white solid: mp, 118.0-120.0°C; ^{13}C NMR ($CDCl_3$) δ 153.8, 131.6, 128.0, 122.9, 112.3, 111.9, 111.8, 101.0, 68.5, 56.0, 53.1, 44.7, 32.4, 25.0; $[\alpha]^{25}_D$ = -44° ($CHCl_3$, c=1.0). Anal. calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88, N, 12.16. Found: C, 72.65; H, 7.91; N, 12.06.

F. (R,S)-5-Methoxy-3-(N-methylazetidin-2-ylmethyl)-1H-indole

(R,S)-3-(N-Benzyloxycarbonylazetidinyl-2-ylcarbonyl)-5-methoxy-1H-indole was used. The chromatographic eluent was 10% triethylamine in ethyl acetate to afford the title compound as a white solid: mp, 116.0-119.0°C; Anal. calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.61; H, 7.99; N, 12.10.

EXAMPLE 2

1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene or 1-(N-Benzyloxycarbonylpiperid-2-yl)-3-hydroxypropene

To a stirred solution of either ethyl 3-(N-benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate or ethyl-3-(N-benzyloxycarbonylpiperid-2-yl)-2-propenoate (R, or S, or racemate, 10.00 mmol) in anhydrous tetrahydrofuran (75 mL) at -78°C under nitrogen was added dropwise a solution of diisobutylaluminium hydride (1.0 M in hexanes, 12.0 mL, 22.0 mmol, 2.2 eq). The resulting solution was stirred at -78°C under nitrogen for 30 minutes. The reaction solution was then allowed to warmed to room temperature over the course of 2 hours. A saturated solution of sodium hydrogen carbonate (50 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 x 50 mL). The extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residue with diethyl ether/hexanes [1:1] afforded either 1-(N-benzyloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene or 1-(N-benzyloxycarbonylpiperid-2-yl)-3-hydroxypropene.

Following the procedure the following compounds were prepared:

A. **(R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene**

(R)-Ethyl 3-(N-benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate was used. Chromatography of the extraction residue afforded the title compound as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 7.40-7.25 (m, 5H), 5.75-5.53 (m, 2H), 5.20-5.00 (m, 2H), 4.38 (br m, 1H), 4.06 (br d, J=13.7 Hz, 2H), 3.45 (br t, J=7.0 Hz, 1H), 2.03-1.68 (m, 4H); $[\alpha]^{25}_D$ = +34° (MeOH, c=1.0); HRMS: calculated for $C_{15}H_{19}NO_3$ 261.1365, found 261.1356.

B. **(R,S)-1-(N-Benzyloxycarbonylpiperid-2-yl)-3-hydroxypropene**

(R,S)-Ethyl 3-(N-benzyloxycarbonylpiperid-2-yl)-2-propenoate was used. Chromatography of the extraction residue afforded the title compound as a clear, colorless oil: LRMS (m/z, relative intensity) 257 (3), 212 (12), 193 (8), 175 (65), 173 (100), 145 (27), 109 (24), 91 (87); ^1H NMR ($CDCl_3$) δ 7.40-7.20 (m, 5H), 5.70-5.61 (m, 2H), 5.14 (d, J=17.6 Hz, 1H), 5.10 (d J=17.5 Hz, 1H), 4.88 (br m, 1H), 4.14-4.00 (m, 3H), 2.91 (br t, J=12.7 Hz, 1H), 1.78-1.47 (m, 6H). Anal. calcd. for $C_{16}H_{21}NO_3 \cdot 0.1\ H_2O$: C, 69.34; H, 7.71; N, 5.05. Found: 69.38; H, 7.84; N, 5.16.

EXAMPLE 3

Synthesis of Ethyl 3-(N-Benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate or Ethyl 3-(N-Benzyloxycarbonylpiperid-2-yl)-2-propenoate

To a stirred solution of N-carbobenzyloxypyrrolidine-2-carboxaldehyde or N-carbobenzyloxypiperidine-2-carboxaldehyde (5.00 mmol) [S. Kiyooka, et al., J. Org. Chem., 5409 (1989) and Y. Hamada, et al., Chem. Pharm. Bull., 1921 (1982)] in anhydrous tetrahydrofuran at -78°C was added (carbethoxymethylene)triphenylphosphorane (2.09 g, 6.00 mmol. 1.2 eq) as a solid portionwise. The resulting reaction mixture was stirred at room temperature under nitrogen for 2 hours, and then heated at reflux under nitrogen for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was column chromatographed using silica gel (approximately 100 g) and elution with 20% diethyl ether in hexanes afforded either ethyl 3-(N-benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate or ethyl 3-(N-benzyloxycarbonylpiperid-2-yl)-2-propenoate.

A. **(R)-Ethyl 3-(N-Benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate**

(R)-N-Carbobenzyloxypyrrolidine-2-carboxaldehyde was used. Chromatography as described above afforded the title compound as a clear, colorless oil: ^1H NMR ($CDCl_3$-d_6) δ 7.34-7.25 (m, 5H), 6.89-6.76 (m, 1H), 5.88-5.74 (m, 1H), 5.18-5.05 (m, 2H), 4.60-4.43 (m, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.55-3.40 (m, 2H), 2.11-2.00 (m, 1H), 1.90-1.75 (m, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) [Note: due to slow nitrogen inversion two conformers of the products are seen by NMR spectroscopy] δ 166.3, 154.7, 147.9, 147.4, 136.6, 128.4, 127.9, 120.9, 66.9, 65.8, 60.4, 58.1, 57.7, 46.8, 46.4, 31.6, 30.8, 23.6, 22.8, 22.6, 15.3, 14.2.

B. **(R,S)-Ethyl 3-(N-Benzyloxycarbonylpiperid-2-yl)-2-propenoate**

(R,S)-N-Carbobenzyloxypiperidine-2-carboxaldehyde was used. Chromatography as described above afforded the title compound as a clear, colorless oil: ^1H NMR ($CDCl_3$-d_6) δ 7.36-7.27 (m, 5H), 6.85 (dd, J=4.4 and 16.3 Hz, 1H), 5.80 (dd, J-2.4 and 16.3 Hz, 1H), 5.11 (s, 2H), 5.01 (br m, 1H), 4.17 (q, J=6.7 Hz, 2H), 4.05 (br d, J=12.6 Hz, 1H), 2.87 (br

t, 1H), 1.80-1.35 (m, 6H), 1.27 (t, J=6.6 Hz, 3H); FAB LRMS (m/z, relative intensity) 318 ([MH+], 100), 274 (86), 228 (14), 210 (21), 182 (43), 138 (32).

EXAMPLE 4

General Synthesis of Allylsulphonamides

A. **Allylsulphonamide**

The title compound was prepared by the method of M. A. Belous and I. Ya. Postouski, Zhur. Obschei. Khim., 1950, 20, 1701.

B. **N-Methylallylsulphonamide**

The title compound was prepared by an analogous procedure to above by using methylamine instead of ammonia. Anal. calcd. for $C_5H_{11}NO_2S$: C,40.25; H,7.43; N,9.38. Found: C,40.51; H,7.37; N,9.70.

EXAMPLE 5

Preparation of Ethylallylsulphone

The title compound was prepared by the method of R. J. Palmer and C. J. M. Stirling., J. Amer. Chem. Soc., 1980, 102, 7888.

EXAMPLE 6

General Synthesis of Vinyl Sulphonamides

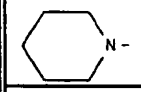
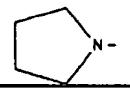
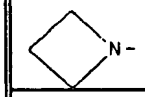
Where the required vinylsulphonamide was not commercially available, they were prepared by the following procedure based on the procedure described in Zhur. Obschei. Khim., 1959, 29, 1494.

A. **N,N-Dimethylvinylsulphonamide**

To a stirred solution of chloroethylsulphonyl chloride (25 g, 153 mmol) in dry diethyl ether (150 mL) at -10°C, was added dropwise a solution of dimethylamine (30.5 mL, 460 mmol) in dry diethyl ether (100 mL) over 5 minutes. After stirring for 90 minutes at -10°C the solution was filtered and evaporated in vacuo. The residue was distilled to give the title compound (9.5 g, 46%): b.p. 120-122°C (20 mm Hg). Anal. calcd. for $C_4H_9NO_2S$: C,35.54; H,6.71; N,10.36%. Found: C,35.36; H,6.37; N,10.19.

B. The following examples were prepared by the general procedure above, using the appropriate amine starting material. Purification was by distillation or column chromatography.

R_2NSO_2-CH=CH_2

R_2N	Isolated Form	Analysis % (Theoretical in brackets) C	H	N
MeNH-	Oil b.p. 93-5°C (0.05 mm Hg)	Literature compound U.S. 3,761,473		
	Oil	47.97 (47.97	7.41 7.48	7.81 7.99)
	Oil	44.73 (44.70	6.80 6.88	8.62 8.69)
nPr_2N-	Oil	50.37 (50.23	8.79 8.96	7.68 7.32)
nPrNH-	Oil	40.22 (40.24	7.35 7.43	9.1 9.39)
	Oil	40.51 (40.79	5.85 6.16	9.35 9.52)
iPrNH-	Oil	40.42 (40.25	7.33 7.43	9.30 9.39)

EXAMPLE 7

General Synthesis of Vinyl Sulphones

Where the required vinyl sulphone was not commercially available, they were prepared from the corresponding thiols using the procedure described by J. M. Gaillot, Y Gelas-Mialhe and R. Vessiere Can. J. Chem., 1979, 57, 1958. The following examples are representative.

RS-CH_2CH_2-OH			
R	Isolated Form	Analysis % (Theoretical in brackets)	
		C	H
nPr	Oil 1/16 EtOAc 1/5 H_20	48.68 (48.76)	9.79 (10.06)
nBu	Oil	T.l.c -Rf. 0.26 ($Si0_2$, Ether/Hexane 1:1)	

$RS-CH_2CH_2-Cl$			
R	Isolated Form	Analysis % (Theoretical in brackets)	
		C	H
nPr	Oil 1/5 H_2O 1/30 CH_2Cl_2	41.63 (41.65)	7.60 (7.69)
nBu	Oil 1.0 H_20	42.31 (42.21)	7.84 (8.27)

$RSO_2-CH_2CH_2Cl$			
R	Isolated Form	Analysis % (Theoretical in brackets)	
		C	H
nPr	Oil	34.75 (35.19)	6.68 (6.50)
nBu	Oil 1/15 CH_2Cl_2	38.41 (38.27)	7.01 (6.95)

$RSO_2-CH=CH_2$			
R	Isolated Form	Analysis % (Theoretical in brackets)	
		C	H
nBu	Oil	48.95 (48.62)	8.07 (8.16)

EXAMPLE 8

4-(Nitrophenyl)methanesulphonyl chloride

To a stirred solution of sodium thiosulphate (72.0g, 0.291 mol) in water (75 mL) and methanol (50 mL) was added at room temperature, over 5 minutes, 4-nitrobenzyl chloride (50.0g, 0.291 mol). The resulting reaction mixture was heated to reflux and stirred, at reflux, for a further 2.25 hours. The reaction mixture was then cooled down and evaporated under reduced pressure, azeotropin with toluene to give a white solid (150 g). The white solid was added to a mixture of acetic acid (75 mL), water (100 mL) and ice, the reaction mixture cooled to 0°C and chlorine gas passed through the system for 1.25 hours, maintaining the reaction temperature below 10°C throughout. The excess chlorine gas was removed by purging the reaction mixture with nitrogen gas for 1.25 hours. The resulting slurry was filtered, drying the solid thus obtained in air. The title compound thus obtained (60.5 g) was used as such in Example 37 without further purification or characterization.

EXAMPLE 9

4-t-Butylaminosulphonylmethylnitrobenzene

To a cooled (ice bath) solution of t-butylamine (48.45 mL, 461 mmol) in dichloromethane (500 ml) was added dropwise, with stirring, a solution of the product of Example 36 (54.33 g, 231 mmol) in dichloromethane (500 mL). This addition was carried out over 15 minutes with the temperature maintained below 10°C throughout. The reaction was then allowed to warm to room temperature and stirred for a further 12 hours. The reaction was then diluted with water (200 mL), the organic layer separated, washed sequentially with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the product as a brown solid. Recrystallization of the brown solid from ethanol gave the title

compound as a white solid (49.0 g): mp, 156-158°C; TLC (dichloromethane/methanol 30:0.4): Rf = 0.66. ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 2H), 7.6 (d, 2H), 4.40 (s, 2H), 4.10 (s, 1H), 1.38 (s, 9H). Anal. calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.55; H, 5.97; N, 10.30. Found: C, 48.53; H, 5.92; N, 10.29.

EXAMPLE 10

4-t-Butylaminosulphonylmethylaniline

A solution of the product of Example 37 (1.17 g, 4.29 mmol) in absolute ethanol and 10% palladium on carbon (0.32 g) was stirred under a hydrogen atmosphere (60 psi) at 60°C for 66 hours. The mixture was filtered through CELITE filter aid and the resulting solution evaporated under reduced pressure to give the product as a solid. Recrystallization from ethanol gave the title compound as a white solid (0.95 g): mp, 137-138°C; TLC (dichloromethane/methanol 30:0.4): Rf = 0.43. ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 2H), 6.65 (d, 2H), 4.15 (s, 2H), 3.95 (br s, 1H), 3.75 (br s, 2H), 1.32 (s, 9H). Anal. calcd. for $C_{11}H_{18}N_2O_2S$: C, 54.51; H, 7.49; N, 11.56. Found: C, 54.76; H, 7.60; N, 11.43.

EXAMPLE 11

4-(t-Butylaminosulphonylmethyl)-2,6-dibromoaniline

To a stirred solution of the product of Example 38 (0.77 g, 3.17 mmol) in dichloromethane (15 mL) and methanol (15 mL) was added sodium bicarbonate (0.80 g, 9.53 mmol) with stirring, at 20°C. Bromine (0.315 mL, 6.11 mmol) was then added dropwise, to the resultant slurry. The resulting mixture was then stirred for 18 hours concentrated in vacuo and taken up in ethyl acetate/water (1:1). The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were then washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the product as a white solid. Recrystallization from hexane/ethyl acetate gave the title compound as a white solid (1.15 g). Mp 140-142°C; TLC (dichloromethane/methanol 30:0.4): Rf = 0.60. ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 2H), 4.65 (br s, 2H), 4.05 (s, 2H), 4.00 (s, 1H), 1.40 (s, 9H). Anal. calcd. for $C_{11}H_{16}N_2O_2SBr_2$: C, 33.02; H, 4.03; N, 7.00. Found: C, 33.52; H, 4.04; N, 6.92.

EXAMPLE 12

4-t-Butylaminosulphonylmethyl-2,6-dibromo-N-trifluoroacetylaniline

To a stirred solution of the product of Example 39 (1.01 g, 2.52 mmol) and pyridine (0.26 mL, 3.28 mmol, 1.30 eq) in anhydrous methylene chloride (15 mL) at 0°C under a nitrogen atmosphere was added dropwise trifluoroacetic anhydride (0.38 ml, 2.68 mmol, 1.1 eq). The resultant reaction mixture was stirred at 0°C, under a nitrogen atmosphere, for 1 hour. The reaction mixture was then diluted with dichloromethane (150 mL), washed with water (2 x 50 mL) and dried ($MgSO_4$). Evaporation under reduced pressure gave a white solid which was recrystallized from hexane/diethyl ether to give the title compound as a white solid (1.10 g). Mp 166-167°C; TLC (dichloromethane/methanol 30:0.4): Rf = 0.21. ^{1}H NMR ($CDCl_3$) δ 7.75 (br s, 1H), 7.70 (s, 2H), 4.20 (s, 2H), 4.10 (s, 1H), 1.45 (S, 9H). Anal. calcd. for $C_{13}H_{15}N_2O_3SBr_2F_3$: C, 31.48; H, 3.05; N, 5.65. Found: C, 31.41; H, 3.11, N, 5.55.

EXAMPLE 13

(R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-[N-(4-t-butylaminosulphonylmethyl-2,6-dibromophenyl)-N-trifluoroacetylamino]propene

To a stirred solution of the product of Example 40 (28.0 g, 56.0 mmol) and triphenylphosphine (15.0 g, 86.0 mmol, 1.53 eq) in anhydrous tetrahydrofuran (70 mL), under a nitrogen atmosphere, at 10°C, was added dropwise a solution of diethylazodicarboxylate (8.9 mL, 56 mmol) in anhydrous tetrahydrofuran (15 mL). The reaction solution was then warmed to 25°C and stirred for a further 25 minutes whereupon a solution of the product of Example 12A (14.79 g, 57.0 mmol) in anhydrous tetrahydrofuran (45 mL) was added dropwise, over 10 minutes. The reaction solution was then stirred at 25°C, under a nitrogen atmosphere for 18 hours. The resulting reaction solution was evaporated under reduced pressure, triturated with diethyl ether, filtered and the filtrate evaporated under reduced pressure and the residue was column chromatographed using silica gel (approximately 850 g), eluting with an ethyl acetate gradient in hexanes to afford the title compound as a white foam. TLC (hexane/ethyl acetate 1:1): Rf = 0.65. ^{1}H NMR ($CDCl_3$) [Note: due to slow nitrogen inversion two conformers of the products are seen by NMR spectroscopy] δ 7.50-7.80 (m, 2H), 7.25 - 7.42 (m, 5H), 5.42-5.65 (m, 2H), 5.30 (s, 0.14H), 5.00-5.20 (m, 2H), 4.02-4.55 (m, 6H), 3.28-3.45 (m, 2H), 1.25-1.90 (m, 13H). Anal. calcd. for $C_{28}H_{32}N_3O_5SBr_2F_3$. 7/100 CH_2Cl_2: C, 45.23; H, 4.34; N, 5.64. Found: C, 45.06; H, 4.44; N,

5.87.

EXAMPLE 14

(R)-3-(N-Benzyloxycarbonylpyrrolidin-2-ylmethyl)-7-bromo-5-(t-butylaminosulphonylmethyl)-1H-indole

To a stirred solution of the product of Example 41 (29.90 g, 40.44 mmol) in 1,2-dimethoxyethane (160 mL) under a nitrogen atmosphere, at 20°C was added palladium (II) acetate (0.97 g, 4.32 mmol) followed by tetrabutylammonium chloride hydrate (11.25 g, 40.48 mmol) and triethylamine (22.3 mL, 160 mmol). The reaction solution was stirred for a further hour at 20°C and then heated at reflux for 18 hours. The reaction solution was then allowed to cool to 20°C, evaporated under reduced pressure, taken up in ethyl acetate (800 mL) and washed with water. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a dark brown foam. Column chromatography using elution with 10% acetone in dichloromethane failed to provide a more pure title compound. The resulting crude product (21.3 g of an off-white foam) was used as such in the preparation of Example 43.

EXAMPLE 15

(R)-7-Bromo-5-(t-butylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

To a stirred suspension of lithium aluminum hydride (7.07 g, 186 mmol) in anhydrous tetrahydrofuran (100 mL), at 0°C, under a nitrogen atmosphere, was added dropwise, over 30 minutes, a solution of the resulting product of Example 42 (21.3 g) in anhydrous tetrahydrofuran (100 mL). The resulting mixture was allowed to warm to room temperature and then stirred for a further 56 hours. The reaction was then cooled to 0°C and cautiously treated with water (7.0 mL), followed by 15% aqueous sodium hydroxide solution (7.0 mL), and then with more water (21.0 mL). The resulting black precipitate was removed by filtration, washing with ethyl acetate. The filtrate was then washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products as a gum. This was column chromatographed using silica gel (50 g) and elution with dichloromethane/methanol (100:5) followed by dichloromethane/methanol/ammonium hydroxide (90:10:1) to afford the title compound (9.9g) as a white foam. TLC (dichloromethane/methanol/ammonium hydroxide 90:10:1): Rf = 0.33. ^{1}H NMR ($CDCl_3$) δ 8.35 (br s, 1H), 7.52 (s, 1H), 7.40 (s, 1H), 7.12 (s, 1H), 4.30 (s, 2H), 4.00 (s, 1H), 3.12-3.25 (m, 2H), 2.60-2.72 (m, 1H), 2.50-2.10 (m, 1H), 2.49 (s, 3H), 2.22-2.38 (m, 1H), 1.55-1.78 (m, 4H), 1.39 (s, 9H). $[\alpha]^{25}_D$ = + 47° (CH_3OH, c=0.1). Anal. calcd. for $C_{19}H_{28}N_3O_2SBr$: C, 51.59; H, 6.38; N, 9.50. Found: C, 51.84; H,6.52; N, 9.52.

EXAMPLE 16

2,6-Dibromo-4-methylaminosulfonylmethylaniline

To a stirred solution of 4-methylaminosulfonylmethylaniline (10 g) in a mixture of methylene chloride (100 mL) and methanol (200 mL) was added sodium bicarbonate (12.6 g) followed by bromine (16 g) in methylene chloride (80 mL). Then the reaction mixture was evaporated in vacuo and the residue partitioned between ethyl acetate (200 mL) and water (100 mL). The ethyl acetate phase was washed with water and brine then dried and evaporated to give the title compound as a brown solid (17.1 g). Mp 155-157°C. ^{1}H NMR ($CDCL_3$) δ 7.4 (s, 2H), 4.6 (bs, 2H), 4.1 (m, 3H), 2.75 (d, 3H).

EXAMPLE 17

2,6-Dibromo-4-methylaminosulfonylmethyl-N-trifluoroacetylaniline

2,6-Dibromo-4-methylaminosulfonylmethylaniline (410 g) was stirred in methylene chloride (8 L) containing pyridine (118 g) and treated with trifluoroacetic anhydride (307.5 g) in methylene chloride (300 mL). Upon complete consumption of the aniline the reaction mixture was diluted with methylene chloride (2 L) and with water (5 L) resulting in precipitation of the title compound (281.9 g) which was removed by filtration. mp 179-180°C. TLC (EtOAc/hexane 1:1): Rf = 0.3. Anal. calcd. for $C_{10}H_9Br_2F_3N_2O_3S$: C 26.45; H, 2.00; N, 6.17. Found C 26.46; H, 1.79; N, 6.12.

Further title compound (165 g) was recovered by crystallization from the (water-washed) combined filtrate and washes upon concentration.

EXAMPLE 18

(R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene

To a stirred solution of (R)-ethyl 3-(N-benzyloxycarbonylpyrrolidin-2-yl)-2-propenoate (574 g) in tetrahydrofuran (5.7 L) at about -78°C was added boron trifluoride etherate (295.4 g) and then diisobutylaluminum hydride (1.5 M in toluene, 3.91 L, 3.1 eq) added (over two hours) maintaining the temperature below -62°C. The resulting solution was stirred (between -78 and -62°C) for three hours and then quenched into aqueous citric acid solution (2 kg citric acid in 5 L water plus 4 L ice) over about 40 minutes. The phases were separated and the aqueous phase extracted with ethyl acetate (2 x 2.1 L). The combined organic solution was dried (over magnesium sulphate) and evaporated, then the residual oil purified by chromatography through silica gel, eluting with mixed ethyl acetate/hexane (9:1 to 4:1) to give the title compound as an oil (260 g), as produced in Example 12A (as an alternative, the residual oil can be purified by chromatography through silica gel eluting with ethyl acetate:hexane (1:1)).

EXAMPLE 19

(R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-[N-(4-methylaminosulfonylmethyl-2,6-dibromophenyl)-N-trifluoroacetylamino]propene

Triphenylphosphine (5.71 g) was dissolved in anhydrous tetrahydrofuran (30 mL) and, in an ice bath, diethylazodicarboxylate (3.71 g in 20 mL anhydrous THF) was added dropwise. Having removed the ice-bath, the reaction mixture was diluted with a further 20 mL anhydrous THF, followed by 2,6-dibromo-4-methylamino-sulfonylmethyl-trifluoroacetylaniline (6.45 g in 50 mL anhydrous THF), and (R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-hydroxypropene (5.51 g in 30 mL anhydrous THF) added dropwise. When conversion was judged complete the reaction mixture was evaporated in vacuo (onto silica gel - 20 g) and purified by column chromatography (SiO_2 - 1.6 kg) eluted with 5% acetone in methylene chloride to give the title compound as a colorless foam (9.13 g). TLC (methylene chloride/acetone 9:1) Rf = 0.60; Anal. calcd. for $C_{25}H_{26}Br_2F_3N_3O_5S$ C 43.1; H, 3.7; N, 6.0. Found C, 43.93; H, 3.99; N, 6.00.

Similarly, the reaction may be conducted in 1,2-dimethoxyethane solvent and processed without purification to directly yield the compound of Example 52 under standard Heck coupling conditions (in mixed 1,2-dimethoxyethane with N,N-dimethylformamide).

EXAMPLE 20

(R)-3-(N-Benzyloxycarbonylpyrrolidin-2-ylmethyl)-7-bromo-5-(methylaminosulfonylmethyl)-1H-indole

(R)-1-(N-Benzyloxycarbonylpyrrolidin-2-yl)-3-[N-(4-methylaminosulfonylmethyl-2,6-dibromophenyl)-N-trifluoroacetylamino]propene (9.00 g) in triethylamine (70 mL) containing N,N-dimethylformamide (20 mL), tetra-n-butylammonium chloride (3.61 g) and palladium acetate (1.01 g) was heated at 80°C until conversion was complete. The cooled reaction mixture was filtered through CELITE and washed with methylene chloride. The combined filtrate and washings were then evaporated in vacuo onto silica gel (15 g) then purified by column chromatography (SiO_2 - 1.6 kg) eluted with 4% acetone in chloroform. The product-rich fractions were combined and evaporated then re-purified by crystallization from a mixture of diethyl ether (50 mL) and methylene chloride (10 mL). The title compound was recovered by filtration (washing with hexanes) as a colorless solid (2.40 g). TLC (methylene chloride/acetone 10:1) Rf = 0.35; Anal. calcd. for $C_{23}H_{26}BrN_3O_4S$: C, 53.1; H, 5.0; N, 8.1. Found C, 53.13; H, 5.0; N, 7.8.

Further title compound (2.03 g) was recovered from the crystallization liquor upon evaporation and purification by silica chromatography (300 g SiO_2 eluted with diethyl ether).

EXAMPLE 21

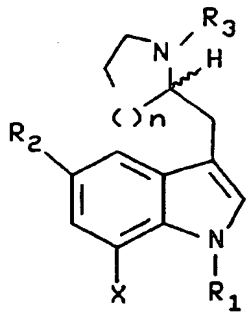
(R)-7-Bromo-5-(methylaminosulfonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole

To a chilled suspension of lithium aluminum hydride (47.89 g) in tetrahydrofuran (938 mL), (R)-3-(N-benzyloxycarbonylpyrrolidin-2-ylmethyl)-7-bromo-5-(methylaminosulfonylmethyl)-1H-indole (262.7 g) in tetrahydrofuran (1250 mL total) was added slowly dropwise. The reaction mixture was stirred at ambient temperature and then warmed to 40°C until conversion was complete. Then, the mixture was cooled and quenched by slow addition of industrial methylated spirit (160 mL), followed by 4M aqueous sodium hydroxide solution (45 mL), then water (142 mL). The mixture was then filtered (through Arbacel). The filtered solids were reslurried in hot industrial methylated spirit (1600 mL) then refiltered. The filtered solids were then washed with a further portion of industrial methylated spirit (200 mL) and then again reslurried from hot industrial methylated spirit (1600 mL). The resultant slurry was again re-filtered. The combined filtrates

and washings were evaporated in vacuo to give a crude oil which was stirred in mixed water (1000 mL) / ethyl acetate (1000 mL). The aqueous phase was separated and washed with ethyl acetate (500 mL) (then the aqueous discarded) and then the ethyl acetate extracts combined and diluted with water (1000 mL) and the whole acidified (by addition of concentrated hydrochloric acid). The aqueous phase was separated and the organic phase washed with water (500 mL). These two aqueous phases were combined and made basic (by addition of 40% aqueous sodium hydroxide solution) and the product re-extracted with ethyl acetate (2x1000 mL), then again at pH9 with further ethyl acetate (500 mL). The combined ethyl acetate extracts were evaporated to an oil then re-evaporated from acetone (250 mL) to give the title compound (200.7 g) as a semi-solid mass. TLC (diethyl ether/ethyl acetate/methanol/diethyl amine 50:50:5:5): Rf = 0.26. ^{1}H NMR (d_6 DMSO) δ 11.05 (s, 1H), 7.5 (s, 1H), 7.3 (s, 1H), 7.2 (s, 1H), 6.85 (q, 1H), 4.35 (s, 2H), 2.95 (m, 2H), 2.55 (d, 3H), 2.5 (m, 1H), 2.35-2.3 (m, 1H and s, 3H), 2.1 (m, 1H), 1.75-1.4 (m, 4H).

Claims

1. A compound of the formula



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wherein n is O, 1, or 2; X is chlorine, bromine, or iodine; R_1 is hydrogen; R_2 is selected from hydrogen, halogen, cyano, $-OR_4$, $-(CH_2)_m-(C=O)NR_5R_6$, $-(CH_2)_m-SO_2NR_5R_6$, $-(CH_2)_m-NR_7(C=O)R_8$, $-(CH_2)_m-NR_7SO_2R_8$, $-(CH_2)_m-S(O)_xR_8$, $-(CH_2)_m-NR_7(C=O)NR_5R_6$, $-(CH_2)_m-NR_7(C=O)OR_9$, and $-CH=CH(CH_2)_yR_{10}$; R_3 is selected from hydrogen and C_1 to C_6 linear or branched alkyl; R_4 is selected from hydrogen, C_1 to C_6 alkyl, and aryl; R_5 and R_6 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl or R_5 and R_6 taken together to form a 4, 5, or 6 membered ring; R_7 and R_8 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_9 is selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_{10} is selected from $-(C=O)NR_5R_6$ and $-SO_2NR_5R_6$, wherein R_5 and R_6 are defined as above, and $-NR_7(C=O)R_8$, $-NR_7SO_2R_8$, $-NR_7(C=O)NR_5R_6$, $-S(O)_xR_8$ and $-NR_7(C=O)OR_9$, wherein R_7, R_8, and R_9 are as defined above; y is 0, 1, or 2; x is 1 or 2; m is 0, 1, 2, or 3; and the above aryl groups and the aryl moieties of the above alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C_1 to C_4 alkoxy, with the proviso that when R_2 is hydrogen or $-OR_4$ and R_4 is hydrogen, n is 0 or 1, and the pharmaceutically acceptable salts thereof.

2. The R enantiomer of a compound according to claim 1.

3. A compound according to claim 1 wherein R_1 is hydrogen; R_2 is $-(CH_2)_m-SO_2NHR_5$, $-(CH_2)_m-NHSO_2R_8$, $-(CH_2)_m-SO_2R_8$, $-(CH_2)_m-(C=O)NHR_5$, or $-(CH_2)_m-NH(C=O)R_8$; R_3 is hydrogen or methyl; and m, R_5 and R_8 are as defined in claim 1.

4. A compound according to claim 1, said compound being selected from:
(R)-7-Bromo-5-(t-butylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole; and
(R)-7-Bromo-5-(methylaminosulfonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

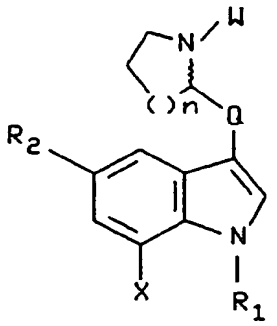
5. A pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission comprising an amount of a compound according to claim 1 effective in treating such a disorder and a pharmaceutically acceptable carrier.

7. A method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

8. A method for treating disorders arising from deficient serotonergic neurotransmission comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such a disorder.

9. A compound of the formula



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wherein X is bromine, chlorine, or iodine; W is $-CO_2R_{11}$ or R_3; Q is CH_2 or C=0; n is 0, 1 or 2; R_1 is hydrogen; R_2 is selected from halogen, cyano, $-OR_4$, $-(CH_2)_m-(C=O)NR_5R_6$, $-(CH_2)_m-SO_2NR_5R_6$, $-(CH_2)_m-NR_7(C=O)R_8$, $-(CH_2)_m-NR_7SO_2R_8$, $-(CH_2)_m-S(O)_xR_8$, $-(CH_2)_m-NR_7(C=O)NR_5R_6$, $-(CH_2)_m-NR_7(C=O)OR_9$, and $-CH=CH(CH_2)_yR_{10}$; x is 1 or 2; m is 0, 1, 2, or 3; R_3 is selected from hydrogen and C_1 to C_6 linear or branched alkyl; R_4 is selected from hydrogen, C_1 to C_6 alkyl, and aryl, R_5 and R_6 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl or R_5 and R_6 taken together to form a 4, 5, or 6 membered ring; R_7 and R_8 are independently selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_9 is selected from hydrogen, C_1 to C_6 alkyl, aryl, and C_1 to C_3 alkyl-aryl; R_{10} is selected from $-(C=O)NR_5R_6$ and $-SO_2NR_5R_6$, wherein R_5 and R_6 are defined as above, and $-NR_7(C=O)R_8$, $-NR_7SO_2R_8$, $-NR_7(C=O)NR_5R_6$, $-S(O)_xR_8$ and $-NR_7(C=O)OR_9$, wherein R_7, R_8, R_9 and x are defined as above; y is 0, 1, or 2; R_{11} is selected from C_1 to C_6 alkyl, benzyl and aryl; and the above aryl groups and the aryl moieties of the above alkyl-aryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C_1 to C_4 alkoxy, with the proviso that when W is R_3, Q is C=O, and with the proviso that when X is bromine, chlorine, or iodine, W is $-CO_2R_{11}$ and Q is CH_2.

10. The R enantiomer of a compound according to claim 9.